Optimising the management of systemic lupus erythematosus

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Update on the management of systemic lupus erythematosus.

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Background: who is at risk and what is the outcome of lupus?

Systemic lupus erythematosus (SLE or lupus for short) is a multisystem, autoimmune disease that can present in women or men at any age but is most common in women in the reproductive age group especially women of African-Caribbean and South Asian descent[1]. Lupus presents increasingly after the age of 40 in Europeans and affected nearly 1 in 1000 of the population in the UK in 2012[1]. The mean age at diagnosis was 48.9 years[1] but was lower in those of African ancestry [1]. These patients of African origin are at increased risk of lupus nephritis which occurs in about one third of UK lupus patients. End-stage renal disease occurred in 20% of lupus nephritis patients in a UK cohort study. The mean age at death was 40.3 years with an average of 7.5 years between death and development of lupus nephritis [2]. Another UK cohort study showed that there is still an increased risk of premature death in women and men with lupus in general, with

a mean age of death of 53.7 years [3]. Most deaths were due to infection or cardiovascular disease and active lupus rarely caused death in the UK[3;4]. In addition lupus causes considerable morbidity as it may present with slowly or rapidly progressive active disease that can lead to the accumulation of chronic damage if not promptly diagnosed, appropriately treated and regularly monitored [5;6].

To optimise these aspects of management and to improve the outcome of this variable and potentially life-threatening disease the British Society of Rheumatology (BSR) published a NICE-accredited guideline for the management of systemic lupus erythematosus in adults in 2018[7]. The full guideline}[8] is available open access online for reference and covers in detail the diagnosis, assessment, and monitoring of lupus and the treatment of mild, moderate and severe active lupus disease. The recommendations are evidence-based following an extensive literature review up to June 2015. The guideline does not cover the evidence for paediatric lupus as there is relatively little literature on paediatric lupus. The target audience includes rheumatologists and other clinicians such as nephrologists, immunologists and dermatologists, trainees in these specialties and emergency medicine, as well as GPs, clinical nurse specialists, and other allied health professionals involved in the care of adult lupus patients[7;8].

How does lupus present clinically?

SLE can present with a large variety of clinical features affecting any system in the body, so making the diagnosis can be a challenging process[9-11]. Delays in diagnosis are well recognised and remain a concern[12]. Some of the most typical mild, moderate and severe features are shown in the Figure. It is important to ensure that the diagnosis of lupus is appropriate before considering treatment [10;11]. Lupus should be considered particularly, but not exclusively, in individuals at increased risk of the disease from African, South Asian and Chinese backgrounds[13]. It is widely recognised that lupus causes fatigue, skin rashes often associated with photosensitivity, hair loss and inflammatory arthritis mainly in women. However it is important to remember that lupus can affect men as well. In fact in men it often results in severe disease including renal involvement and more chronic scarring (damage) compared with women in many studies, possibly due to delayed diagnosis [3;4;14]. Renal and neurological involvement cause a lot of morbidity and mortality [3;4]. Constitutional (e.g. fever and lymphadenopathy) cardio-respiratory (e.g. pleurisy and pericarditis), gastrointestinal (e.g. gall bladder vasculitis) and hepatic (e.g. autoimmune hepatitis) features may occur in up to 60% of patients but are often not recognised as being due to lupus, and need to be distinguished from infection, drug side-effects and other co-morbid conditions including lymphoma[8]. Eye involvement, other than sicca symptoms, is rare but potentially sight-threatening and requires prompt referral to an experienced ophthalmologist[15].

Causes of lupus, drug-induced lupus and immunological manifestations

The clinical features of acute lupus are mostly due to the formation of immune complexes involving autoantibodies that induce complement activation and consumption resulting in inflammatory processes that

affect a variety of organs. Thrombosis associated with anti-phospholipid antibodies may contribute to the pathogenesis in some patients[5;9]. The autoantibodies are produced as a result of a variety of mechanisms including defective clearance of apoptotic cells, excessive B cell activation and proliferation, altered T cell signalling and function, and changes in cytokine profiles with an increasing role for interferon-alpha in recent research [5;16]. There is evidence for underlying genetic susceptibility involving an increasing number of loci (50-100 genes) and pathways with environmental triggers including infections, UV light, hormones such as estrogen, and cigarette smoking. Drug-induced lupus is also recognized and usually resolved in withdrawal of the offending drug, for example tetracyclines, isoniazid, sulphonamides, propylthiouracil, hydralazine, procainamide, phenytoin and anti-TNF therapy[5;17;18]. Anti-TNF may induce autoantibodies such as ANA without inducing lupus disease, however these drugs may also trigger full SLE in susceptible people. The importance of environmental influences is shown by the observation that only in about one in four twin pairs where one twin has SLE do both develop lupus over time.

An autoantibody screen should be performed when there is a clinical suspicion of SLE. Most lupus patients are ANA positive (≤95%). If ANA is negative, there is a low clinical probability of the patient having SLE however a minority have anti-double stranded (ds)DNA or anti-Ro antibody positivity without ANA that will be found when assessed on clinical grounds by a specialist[19]. ANA tests are not specific for the diagnosis of lupus and may occur in a variety of other conditions including Sjögren's syndrome, systemic sclerosis, dermatomyositis, viral infections such as infectious mononucleosis and occur sometimes in patients with cancer[11]. The ANA test can become negative in treated patients and the results can vary with different assays. Anti-dsDNA and anti-Sm antibodies are rare in other conditions but are less sensitive than ANA [9;19-21]. Anti-dsDNA antibodies rise and complement C3 and C4 levels fall with active disease and are useful in monitoring disease as well as diagnosis (Box 1)[7;8].

Anti-Ro and anti-La antibodies are associated with photosensitivity, subacute cutaneous lupus rashes, Sjögren's syndrome and neonatal lupus syndrome including congenital complete heart block in babies[11;22]. Anti-RNP antibodies occur in overlap conditions such as mixed connective tissue disease with myositis and lung involvement[11]. Lupus patients should be tested for anti-phospholipid antibodies as this indicates a group at increased risk of arterial/venous thrombosis and adverse pregnancy outcomes such as 3 or more first trimester miscarriages, late pregnancy losses and pre-eclampsia before 34 weeks gestation [23;24]. Confirmatory tests for antiphospholipid syndrome are positive lupus anticoagulant, anti-cardiolipin antibodies (IgG, IgM), and/or anti-beta-2 glycoprotein-1(IgG, IgM) antibodies on two occasions at least 12 weeks apart[23;24]. The lupus anticoagulant test is the most specific of the 3 tests and is associated with a higher positive predictive value. Triple positivity characterised by positive lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein- I antibodies is associated with a cumulative incidence of thrombosis of 37.1% after 10 years [25].

Diagnosis of lupus and classification criteria

When considering a diagnosis of SLE, a detailed clinical history and examination is required to identify clinical features supported by renal and haematological assessment. A low CRP with a raised ESR is typical of active lupus unless there is infection or effusions. According to the BSR guidelines for lupus[7;8] the diagnosis of SLE requires a combination of clinical features and the presence of at least one relevant immunological abnormality as discussed above. A positive ANA occurs in approximately 5% of adults and has poor diagnostic value in the absence of clinical features of lupus or other autoimmune disease. The American College of Rheumatology (ACR) [26;27] and Systemic Lupus International Collaboration Clinics (SLICC) [28] (table 1) classification criteria are not diagnostic criteria but may be helpful when considering the diagnosis, however they do not cover all the possible clinical manifestations of lupus.

Based on the ACR(previously the American Rheumatism Association) revised criteria for SLE published in 1982[26] and the 1997 modification[27], a patient may be classified as having SLE if they have had 4 or more of 11 criteria at any time. However, not all patients with these criteria have lupus and not all patients diagnosed clinically with lupus have 4 or more of these criteria. The SLICC group devised alternative classification criteria for lupus to overcome these and related issues (Table 1) [28]. The critical difference is that they introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items compared to the traditional ACR criteria[27]. Biopsy proven lupus nephritis in the presence of ANA or anti-dsDNA antibodies may also be classified as lupus without the need for other criteria[28]. Low complement (C3 and/or C4) are included in the serological criteria as they reflect complement consumption due to formation of immune complexes in active lupus disease. Although the SLICC criteria are more intuitive and include evidence for the immunopathological basis of lupus, diagnosis should not be restricted to patients that meet these classification criteria. According to the BSR guidelines for SLE[7;8] a diagnosis of SLE can also be made in the presence of other lupus manifestations in the appropriate serological context and should not be made if features are better explained by an alternative diagnosis (such as a different systemic autoimmune disease, infection or cancer).

Clinical assessment of SLE patients

Clinical assessment should include detailed history and review of systems, ideally with full clinical examination including urinalysis in order to determine whether symptoms and signs may be due to lupus disease activity, accumulated damage due to the effects of the disease or its treatment such as lung fibrosis or atherosclerosis, drug toxicity and/or the presence of co-morbidity. Fatigue is very common but non-specific as it can be hard to distinguish whether the cause is lupus itself or if there is another autoimmune condition such as hypothyroidism, anaemia due to iron deficiency (not haemolysis from lupus), fibromyalgia which can co-exist with lupus in up to 30% of patients or physical deconditioning.

Haematological, biochemical, immunological and imaging tests help to determine whether new disease features are due to active inflammation, thrombosis or co-morbidity such as infection. This is an important distinction as this will affect the need for specialist review and future treatments. Antiphospholipid antibodies are associated with thrombotic events, damage and adverse outcomes in pregnancy and should be re-evaluated prior to pregnancy or surgery, and when there is a new severe manifestation or vascular event even if the tests were negative previously. Patients may need referral for skin or renal biopsies to ensure that lupus is the cause of the manifestations before starting definitive treatment. Advice about further assessment and treatment should be sought from relevant hospital specialists such as rheumatologists, nephrologists, haematologists and specialist obstetricians depending on the extent of disease activity and whether planning pregnancy or not. Mild disease activity is clinically stable lupus with no life-threatening organ involvement (see Figure). Patients with moderate disease activity have more serious manifestations requiring more intense immunosuppression and severe disease is defined as organ or life threatening. With an increase in disease activity (termed lupus flare) it can be helpful to consider the likely triggers such as exposure to sunlight, concurrent or recent infection, hormonal changes, and any recent drug change as this will guide further investigation, current treatment change and future monitoring.

Monitoring of SLE patients

Patients with lupus should be monitored regularly for disease features, drug toxicity and co-morbidities[7;8]. Depending on the complexity of the disease and the drug therapy this may need to be performed by a hospital specialist e.g. rheumatologist, nephrologist, dermatologist or by the GP or shared care between the relevant teams. Patients with active disease should be reviewed at least every 1-3 months with blood pressure, urinalysis, renal function, liver function tests, anti-dsDNA antibodies, complement levels and full blood count with further tests as necessary (box 1). ESR is usually high and CRP low with active lupus so an increase in CRP should prompt infection screen. Patients with stable low disease activity or in remission may be reviewed less frequently such as 6 to 12 monthly, As lupus disease activity and complications such as atherosclerotic disease, infection and drug side-effects can develop at any time, patients should be monitored indefinitely[7;8]. Anti-Ro and La antibodies are associated with neonatal lupus (including congenital heart block) and should be checked prior to pregnancy but are not helpful for assessing disease activity (box 1). A detailed guide to the interpretation of haematological, renal and other biochemical parameters is included in the text of the BSR guidelines for the management of lupus and is available online[8].

Patients with lupus are at increased risk of infection, atherosclerotic disease, malignancy, osteoporosis and avascular necrosis. Patients should be screened for modifiable risk factors including hypertension, dyslipidaemia, diabetes, high body mass index and smoking annually[7;8]. They should have their vaccination status reviewed and be immunised as appropriate for example against influenza and pneumococcal pneumonia if they are on immunosuppressants (Table 2). Complications of lupus including chronic fatigue,

cardiovascular risk, osteoporosis, infection, and cancer risk should be managed according to national and international guidelines[7;8].

Treatment of SLE

Until recently only prednisolone and hydroxychloroquine were licensed for lupus[5]. There were relatively few trials until the last 15 years but in 2011, belimumab became the first drug to be licensed for the treatment of active lupus for over 50 years[7;29;30]. Much of the evidence supporting the use of drug therapies off-license in lupus comes from observational studies. This evidence is reviewed in the BSR guideline for the management of SLE which divides the treatment of lupus in to 3 sections covering mild, moderate and severe lupus[7;8]. (Figure). There is only summary advice about the use of drugs in the management of pregnant lupus patients as there is already a BSR guideline on the use of drugs in rheumatic diseases in pregnancy and breast-feeding[31;32].

High factor UV-A and UV-B sunscreen are strongly recommended in the treatment and prevention of UV radiation-induced cutaneous lesions supported by good evidence and there is some evidence that this strategy prevents other lupus manifestations. Patients should be advised about sun avoidance and the use of protective clothing[7;8]. There is high quality evidence for the management of mild lupus using the disease modifying drugs hydroxychloroquine and methotrexate. These drugs reduce the need for corticosteroids[7;8]. Prednisolone doses up to 7.5mg/day may be required for maintenance therapy but topical preparations for cutaneous manifestations and intra-articular injections for arthritis are preferred although there is less evidence for their use. Short courses of non-steroidal anti-inflammatory drugs (NSAIDs) may be used for symptomatic benefit but the evidence is weak and the risks are considerable especially in patients with renal disease in whom they are contra-indicated[7;8].

The management of moderate lupus requires specialist advice and will usually involve the use of immunosuppressive, steroid sparing drugs such as azathioprine, mycophenolate mofetil, calcineurin inhibitors (ciclosporin and tacrolimus) or methotrexate with corticosteroids, in addition to hydroxychloroquine and avoidance of UV radiation[7;8]. The aim is to reduce disease activity, prevent further flares and lower the risk of damage accrual due to disease and corticosteroids in patients with features such as arthritis, cutaneous disease, serositis, vasculitis, or cytopaenias not controlled by hydroxychloroquine. Initial doses of prednisolone up to 0.5 mg/kg/day or the use of intramuscular or intravenous doses of methylprednisolone may be required to control active disease but prednisolone should be reduced steadily to a baseline of 7.5mg/day or less and withdrawn later if possible[7;8]. For patients that are refractory to these drugs, patients should be discussed with and/or seen by a regional specialist lupus centre. The biologic drugs belimumab and rituximab may be considered if the patients meet the appropriate criteria for these drugs[7;8]: NICE guidance for the use of belimumab in active autoantibody-positive SLE in adults published in 2016

(https://www.nice.org.uk/guidance/TA397) or the NHS England 2013 interim clinical commissioning policy statement for rituximab in adult SLE patients (http://www.england.nhs.uk/wp-content/upSOAds/2013/09/a13-psa.pdf).

Organ or life-threatening severe lupus disease, for example lupus nephritis or neuropsychiatric lupus, requires treatment by a specialist with intensive immunosuppression followed by prolonged maintenance therapy to prevent relapse[7;8]. This usually involves intravenous methylprednisolone initially but may consist of high dose oral prednisolone (up to 1 mg/kg/day)) to induce remission with mycophenolate mofetil or cyclophosphamide, followed by steroid taper over several months. The biological therapies belimumab and rituximab are considered if patients fail conventional immunosuppressive drugs due to inefficacy or intolerance as described above. Intravenous immunoglobulin and plasmapheresis are rarely used. In some cases there may be a thrombotic component to the clinical features that requires anticoagulation, The evidence is best for the management of lupus nephritis, weaker for neuro-psychiatric disease and is sparse for other specific organ-specific manifestations[7;8].

Organisation of care for SLE patients

GPs should refer patients suspected of suffering from lupus to a physician with experience of managing lupus so that they can confirm the diagnosis, assess the level of disease activity and provide advice on treatment and monitoring of lupus, its complications and side-effects of therapy. Immunosuppressive therapies are challenging to use in patients with lupus due to the risk of adverse events including infection, difficulties with attribution of cytopenias to lupus or cytotoxic drugs, and the need to distinguish disease activity from damage and co-morbid conditions[8]. Shared care agreements may be put in place once patients are established and stable on therapy. SLE patients should have access to a multi-disciplinary team including a variety of specialists including rheumatologists, nephrologists, dermatologists, haematologists, cardiologists, chest physicians, neurologists, obstetricians, nurse specialists, physiotherapists, as well as podiatrists and occupational therapists working as part of collaborative clinical networks involving regional specialist centres, local hospitals and GPs[8]. Patients should be monitored to ensure that they achieve a low level of disease activity if not remission[33;34] using hydroxychloroquine, immunosuppressants and the minimum amount of corticosteroids, in order to reduce accumulating damage from the disease and its treatment[33]. If drug treatment is not working within the expected time frame, it is important to consider adherence to treatment and to get patients reviewed so that drug therapy can be optimised to promote disease control and to reduce the risk of further morbidity and premature death..

It is important for GPs to be involved in ensuring use of sunscreen and sun avoidance, adequate vitamin D_3 intake given the inability to synthesise vitamin D in the skin without UV light exposure, weight control, exercise, not smoking and other measures to reduce atherosclerotic and osteoporosis risk factors, as well as

cancer screening, contraception and pregnancy planning when the disease is under good control on appropriate treatment for conception (box 2)[8].

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ST has been a member of the speakers' bureau for UCB.

Table 1: Clinical and Immunologic Criteria Used in the SLICC Classification Criteria for SLE[28]

Clinical Criteria
1. Acute cutaneous lupus including: lupus malar rash (do not count if malar discoid) bullous lupus toxic epidermal necrolysis variant of SLE maculopapular lupus rash photosensitive lupus rash *in the absence of dermatomyositis* or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias).
2. Chronic cutaneous lupus including: classical discoid rash localized (above the neck) generalized (above and below the neck) hypertrophic (verrucous) lupus lupus panniculitis (profundus) mucosal lupus lupus erythematosus tumidus chilblains lupus discoid lupus/lichen planus overlap
3. Oral ulcers: palate buccal tongue or nasal ulcers *in the absence of other causes, such as vasculitis, Behcet's disease, infection (herpes viruses), inflammatory bowel disease, reactive arthritis, acidic foods*
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) *in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia*
5. Synovitis involving two or more joints, characterized by swelling or effusion or tenderness in 2 or more joints and thirty minutes or more of morning stiffness.
6. Serositis typical pleurisy for more than 1 day or pleural effusions or pleural rub typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion or pericardial rub or pericarditis by EKG *in the absence of other causes, such as infection, uremia, and Dressler's pericarditis*
7. Renal Urine protein:creatinine ratio (or 24 hr urine protein) representing 500 mg of protein/24 hr or Red blood cell casts

8. Neurologic seizures psychosis mononeuritis multiplex *in the absence of other known causes such as primary vasculitis* myelitis peripheral or cranial neuropathy *in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus* acute confusional state *in the absence of other causes, including toxic-metabolic, uremia, drugs*
9. Hemolytic anemia
10. Leukopenia (< 4000/mm^3 at least once) *in the absence of other known causes such as Felty's, drugs, portal hypertension* OR Lymphopenia (< 1000/mm^3 at least once) *in the absence of other known causes such as corticosteroids, drugs and infection*
11. Thrombocytopenia (<100,000/mm^3) at least once *in the absence of other known causes such as drugs, portal hypertension, TTP*

Immunologic Criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range (or > 2 fold the laboratory reference range if tested by ELISA)
3. Anti-Sm
4. Antiphospholipid antibody: any of the following lupus anticoagulant false-positive rapid plasma regain (RPR) medium or high titer anticardiolipin antibody level (IgG, IgM or IgA) anti-$\square_2$ glycoprotein I (IgG, IgM or IgA)
5. Low complement low C3 low C4 low CH50
6. Direct Coombs' test *in the absence of hemolytic anemia*

* Patients can be classified as having SLE if they satisfy 4 of the clinical and immunological criteria including at least one clinical criterion and one immunologic criterion, OR if they have biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies (68).

Table 2: Modifiable risk factors to review at least annually

Infection	Vaccination status
Cardiovascular disease	Hypertension
	Dyslipidaemia
	Diabetes
	High BMI
	Smoking
Malignancy	Routine cancer screening as per national guidelines

Box 1: Measuring autoantibodies in patients with SLE

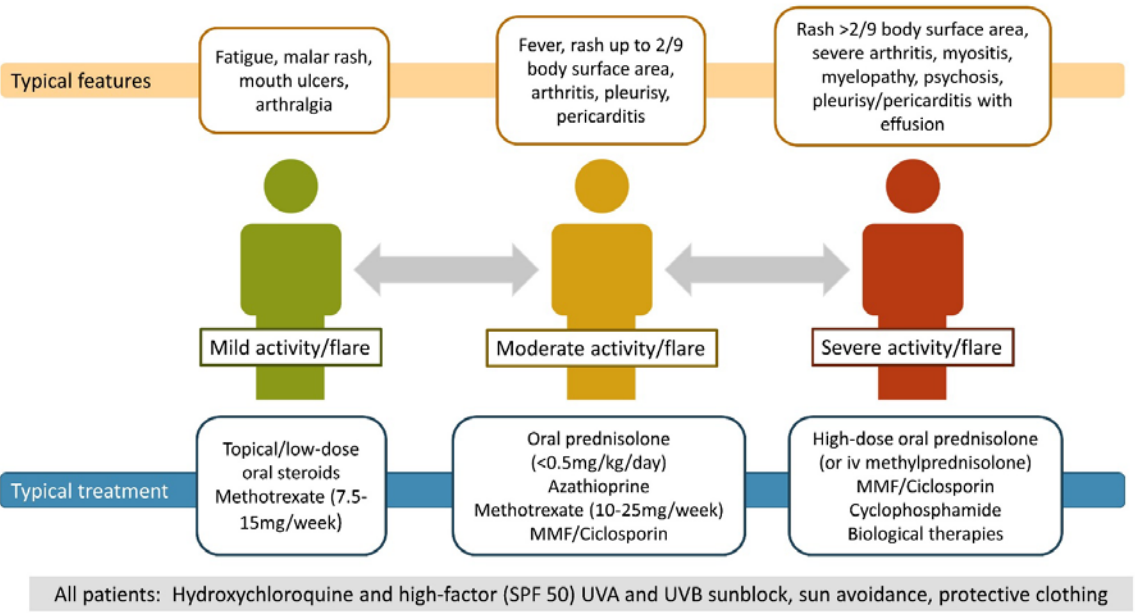
- Increasing Anti-dsDNA antibody levels, and falling C3 and/or C4 complement levels are associated with disease flare.
- ANA, anti-Sm and anti-RNP antibodies do not change with disease activity and should not be routinely measured.
- Measure anti-Ro and anti-La in women planning pregnancy due to risk of congenital heart block (1-2%).
- Check lupus anticoagulant and anti-phospholipid antibodies at baseline and following i) a new vascular event, ii) prior to pregnancy, iii) following an adverse pregnancy outcome.

Box 2: Pregnancy and SLE

- Women with SLE should be referred for pre-pregnancy counselling.
- Pregnancy can increase SLE disease activity and flare. This risk is reduced if the disease is stable for at least 6 months prior to conception.
- Anti-cardiolipin antibodies and lupus anticoagulant antibodies are associated with increased pregnancy loss, preterm birth and intrauterine growth restriction. Specialist advice should be sought.
- Prednisolone, azathioprine, hydroxychloroquine, cyclosporine, tacrolimus, low molecular weight heparin and low-dose aspirin are safe in pregnancy and breast feeding.
- Methotrexate, leflunomide, cyclophosphamide, myophenolate mofetil and biological drugs (rituximab and belimumab) are not safe in pregnancy and should be stopped prior to conception. Seek specialist advice.

Figure: Overview of the management of SLE

Comment [C1]: For information- separate file sent as well



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Practitioner SLE based on BSR guideline 10/05/19 final

Dear Caroline

We were very pleased with your article, please find the proofs attached.

I would be grateful if you could:

* read and check the proofs carefully, particularly all data, the figure, tables, boxes and references
* answer the questions raised at the reviewing and editing stages
* get back to me with your amendments by **2pm Tues May 21. Please drop your corrections into a copy of this email and send it back to me.**

PAGE 17

Editing queries

Byline

Please check that the details are correct for all authors yes

Figure 1

1 Please supply a reference for the diagram Original By JR for this

2 Please obtain permission to reproduce this, if necessary, and supply a credit, if appropriate N/A

GP reviewer's queries

Col 1, 2nd para

'End-stage renal disease occurred in 20% of lupus nephritis patients in a UK cohort study. The mean age at death' for all patients with lupus nephritis was 40.3 years with an average of 7.5 years between the development of lupus nephritis and death.[2]

Comment [CG2]: This was actually only a study of lupus nephritis but I accept that this was not clear

Please rewrite to clarify meaning- done as above

'Another UK cohort study showed that there is still an increased risk of premature death in women and men with lupus in general, with a mean age of death in those that died of 53.7 years. [3]

This sentence is misleading: 382 patients were followed up for up to 21 years during which time 37 patients (9.7% of the cohort) died. Those who died had a mean age at death of 53.7 years. According to Lupus UK "most patients can anticipate a normal lifespan."

Please amend/rewrite to clarify- done as above- I assume that you do not want this expanded to both sentences provided by the reviewer. If you want the longer version suggest "In another UK cohort study, 382 patients were followed up for up to 21 years during which time 37 patients (9.7% of the cohort) died. Those who died had a mean age at death of 53.7 years.

Col 3, 2nd para

'Lupus causes fatigue, skin rashes often associated with photosensitivity, hair loss and inflammatory arthritis mainly in women. However it is important to remember that lupus can affect men as well. In men it often

results in severe disease including renal involvement and more chronic scarring (damage) compared with women in many studies, possibly due to delayed diagnosis. [3;4;14] Renal and neurological involvement cause considerable morbidity and mortality.[3;4] Constitutional (e.g. fever and lymphadenopathy) cardio-respiratory (e.g. pleurisy and pericarditis), gastrointestinal (e.g. gall bladder vasculitis) and hepatic (e.g. autoimmune hepatitis) features may occur in up to 60% of patients but are often not recognised as being due to lupus, and need to be distinguished from infection, drug side effects and other comorbid conditions including lymphoma.[8,] Depression occurs in about 20% of lupus patients but is not usually caused directly by autoimmune disease mechanisms.

A UK primary care study which used the Clinical Practice Research Database identified 1,426 incident cases of SLE (170 males and 1256 females). The most commonly reported symptoms prior to diagnosis were: musculoskeletal (arthritis/arthralgia in 58.6%, myalgia in 8.8%), mucocutaneous (41%, mostly unspecified, 3% maculopapular, 4% discoid) and neurological (depression 20.6%, psychosis 0.04%, seizures 3.1%). The median time from first musculoskeletal symptom to diagnosis was 26.4 months. (Nightingale et al BMJ Lupus 2016;4:issue 1).

Thus from these findings depression appears to be a common presenting symptom whereas psychosis appears to be rare.

1 Do the authors wish to comment on this?

2 When making a diagnosis of major depression, GPs should consider whether it is associated with an underlying condition. I feel that the list of conditions which can present with, or be associated with, depression should include autoimmune rheumatic disorders such as SLE, rheumatoid arthritis and PMR. What do the authors think?

Ed: Please only comment on the CPRD findings and answer the queries if you see fit as strictly speaking they are outside the scope of the brief

Comment [CG3]: I have contributed to a number of publications about neuropsychiatric disease in lupus by the SLICC group (multicentre inception cohort with over 1800 patients recruited by specialist centres within 6 months of diagnosis on average) and taken part in the EULAR neuropsychiatric management recommendations published in Annals of Rheumatic disease in the past. I agree that depression is more common that the conditions in the ACR and SLICC classification criteria and we found about 20% of lupus patients in the SLICC inception cohort study developed mood disorders, mostly depression but consensus is that it is rarely due to lupus autoimmunity and does not improve with immunosuppression in the absence of other lupus features warranting such treatment. I have added a short sentence about this. The Nightingale paper in Lupus Science and Medicine in 2017 acknowledges that they were not able to deal with attribution to lupus and did not say that depression was due to autoimmune disease. There is not space to discuss this here in more detail but it is worth including as suggested.

PAGE 18

Editing queries

Note extra correction needed Table 1: references in title: ref28 is the correct reference source for this table. This table was reproduced in the BSR guidelines ref 8 (but ref 6 is not relevant at all). I would recommend only giving reference 28 at end of the main title of the table- if you want to reference the initial paragraph then it should be reference 28 again, as reference 8 reproduced the information from reference 28 and is not the source of this statement.

Please check table 1 carefully

Please add red circle before subacute cutaneous lupus rash. (“in the absence of dermatomyositis” applied only to the photosensitive lupus rash). All the other items in this section are alternatives (hence the addition of “or” before the last item “subacute cutaneous lupus rash” (which is then described in more details as there are several forms of this rash, as listed in brackets appropriately).

Also col 2 Immunological criteria

4 Re anticardiolipin – IgG, IgM and IgA are specified but IgA is not mentioned in the text in this context (see p19, col 2, 5th para)

Likewise for anti-beta2 glycoprotein 1 IgG, IgM and IgA are specified but IgA is not mentioned in the text in this context

Please amend/clarify for consistency **Suggest leaving as listed as** this is the correct description of the SLICC classification criteria in table 1, as in ref 28 . IgA is not mentioned in the text as we did not discuss it in the BSR guidelines as not widely available in UK, and certainly not available to GPs. Also in the text we

quote and reference the source for the criteria for APS (refs 23 and 24) and they do not mention IgA either. I do not think this is worth explaining as most people will be aware that they cannot request these IgA tests but they may be available in some specialist centres if needed for patients requiring review at some national centres of excellence due to uncertainty about diagnosis or management.

We have written out TTP as thrombotic thrombocytopenic purpura - is this correct? YES

PAGE 19

Editing queries

Col 1 Causes and immunological manifestations

Re anti-TNF should this be anti-TNF-alpha throughout? Yes that is correct (but it is the only version of anti-TNF therapy available and usually just called anti-TNF therapy).

GP reviewer's queries

Col 1, final para

'An autoantibody screen should be performed when there is a clinical suspicion of SLE. Most lupus patients are ANA positive (≥ 95%). If ANA is negative, there is a low clinical probability of the patient having SLE however a minority have anti-double stranded (ds)DNA or anti-Ro antibody positivity without ANA that will be found when assessed on clinical grounds by a specialist[19].

98% of patients will have positive ANA and/or anti-dsDNA antibodies (BSR guideline). Is it appropriate, therefore, for GPs to use a negative ANA plus negative anti-dsDNA antibody result as a rule-out test for SLE? No – true it is very unlikely but not impossible because they can have cytoplasmic anti-Ro or other antibodies mentioned in the SLICC classification criteria (or even less often anti-phospholipid antibodies)- **I do not think that needs adding to the manuscript**. These are cases where a decision would need to be made as to whether a second opinion was needed or not depending on other blood results and clinical features (high esr/low crp/high IgG/cytopenias would all favour lupus). Also antibodies can change over time…

PAGE 20

Editing queries

Table 2 and box 1 – please check carefully

Do either the table or box need a reference? These are both based on text of BSR guideline but not exactly as presented there eg in table 2 : vaccination status and high BMI are not terms mentioned in the text of ref 8 and there was no such table like this (most but not all items/synonims included in a bigger table in ref 8). Box 1 is a summary of some of the recommendations and text in the BSR guideline but this exact format is not written there (but all information is in ref 8).

Col 3, 4th para

'Patients should be screened…annually.' Table 2 says at least annually – do you want to amend the text to be consistent with the table? Yes- good idea- at least annually in both places

GP reviewer's queries

Col 1, 1st para

'Fatigue is very common but non-specific as it can be hard to distinguish whether the cause is lupus itself or if there is another autoimmune condition such as hypothyroidism, anaemia due to iron deficiency (not haemolysis from lupus), fibromyalgia which can coexist with lupus in up to 30% of patients, depression and/or physical deconditioning.'

Fatigue may also be a symptom of depression. A recent meta-analysis found a high prevalence of depression and anxiety in SLE patients: 24% had major depression and 37% had anxiety. (Zhang et al BMC Psychiatry 2017;17:70).

ED: As before only add a brief comment if you see fit - happy to add as suggested in red (comments about depression above and not going to include anxiety as less common problem than depression in other studies but agree it can occur- we have not got space to discuss management of all issues that can occur in lupus patients….)

Col 2, 4th para

'With an increase in disease activity (termed lupus flare) it can be helpful to consider triggers such as sunlight, concurrent or recent infection, hormonal changes, surgery and any recent drug change as this will guide further investigation, treatment and future monitoring.'

I feel that this list of causes of a lupus flare should include surgery. What do the authors think? Happy to add as above but not that common unless drugs are stopped- an issue we have not got space to discuss here!

Col 3, 3rd para

'Patients with lupus are at increased risk of infection, atherosclerotic disease, malignancy, osteoporosis and avascular necrosis.'

How common is avascular necrosis? (A patient of mine had AVN in multiple joints.) **Nil to change**- well recognised but not as common as infection or atherosclerosis or osteoporosis

GP reviewer's queries

PAGE 21

Col 1, 2nd para

'Prednisolone doses up to 7.5mg/day may be required for maintenance therapy but topical preparations for cutaneous manifestations and intra-articular injections for arthritis are preferred although there is less evidence for their use.'

1 I think it is important to keep steroid use to a minimum to reduce the risk of avascular necrosis.

What do the authors think? We say this later - **NIL to add**

2 How common is it for SLE patients to develop other autoimmune conditions? (An SLE patient of mine developed myasthenia gravis.) **Nil to add** - we mention looking for other autoimmune conditions in the context of fatigue eg hypothyroidism (much more common than myasthenic gravis but about 15% develop at least one other autoimmune disease)- no space to discuss in detail.

Organisation of care for SLE patients

'SLE patients should have access to a multidisciplinary team including a variety of specialists including rheumatologists, nephrologists, dermatologists, haematologists, cardiologists, chest physicians, neurologists, obstetricians, nurse specialists, physiotherapists, as well as podiatrists and occupational therapists and clinical psychologists working as part of collaborative clinical networks involving regional specialist centres, local hospitals and GPs.[8],

In view of the high prevalence of anxiety and depression among SLE patients, plus rarer neuropsychiatric complications including psychosis, do the authors think the multidisciplinary team should include a clinical psychologist or psychiatrist? Agree that this was an omission- wish we had more access to clinical psychologists for lupus. Psychiatrists along with all other specialities not mentioned are needed less often and we could list all specialities…. If we could get all newly diagnosed patients to see a clinical psychologist we probably would not have to deal with as much depression, chronic non-specific pain like FM, fatigue etc….

PAGE 21

Editing queries

Competing interests

Please check details and clarify whether John Reynolds has any competing interests - all correct and JR has NONE

PAGES 21/22

Please check all references carefully

Correct page 19 middle column 3rd para end should be 23,24 not 23,2 (after gestation)

Correct page 19 right column 3rd para reference after table 1,p18 should be 28 not 2.

NB we have taken the respective (web) references for the 2 biologics out of the body copy of the text and added them to the ref section as refs 33 and 34. However the link to the NHS England document (now ref 34) does not work so please supply a correct version for this reference

Ref 34 = https://www.england.nhs.uk/wp-content/uploads/2013/09/a13-psa.pdf

Useful information box

Do you wish to add any details of professional bodies, charities or support groups that provide evidence-based information for healthcare professionals and/or patients?

Yes ! Please add:

British Society for Rheumatology guidelines https://www.rheumatology.org.uk/practice-quality/guidelines

Lupus UK the national charity for people affected by lupus https://www.lupusuk.org.uk/

Versus Arthritis information on lupus

https://www.arthritisresearchuk.org/shop/products/publications/patient-information/conditions/lupus.aspx